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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,339	06/18/2007	Robert L. Wolfert	DEX0531US.NP	8696

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EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/588,339	WOLFERT ET AL.	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73,74,76,78,80,82,86-87 and 89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/18/06 and 4/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-4,8,9,12,17,19,22,25-27,30,35,36,39,42-45,48,51,52,55,59,61,64,67-70,73,74,76,78,80-82 and 86-89.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 1-4,8,9,12,17,19,22,25-27,30,35,36,39,42-45,48,51,52,55,59,61,64,67-70,81 and 88.

103 rejections need to be changed.

Response to Election-Restriction

1. Applicants' election with traverse of Group III, claims 73-74, 76, 78, 90-82 and 86-89 filed November 18, 2009 in response to Office Action of September 18, 2009 is acknowledged and entered. Applicants' election with traverse of "2-thio PAF" for a single species of a "substrate" is also acknowledged. The single species for the "substrate" was elected during a telephone conversation with Kathleen A. Tyrrell on 1/28/10 with traverse. Affirmation of this election must be made by applicant in replying to this Office action. Claims 81 and 88 do not read on the elected species and claims 73, 80, 86 and 86 read on the elected species in part wherein the substrate is 2-thio PAF.

   Applicants' traversal for restriction is on the ground that the contacting immobilized Lp-PLA2 with a dubstrate to measure enzymatic activity of Lp-PLA2 is not obvious over the reference because neither these references measure enzymatic activity of immobilized LpPLA2.

   Applicants' arguments have been fully considered but are not persuasive because the Examiner maintains the combination of references teach the detection of immobilized LpPLA2 with a substrate for LpPLA2 for the reasons of record as described in item 2 in the election/restriction requirement mailed 9/18/09. Applicants argued that antibodies have been demonstrated in the art to inhibit the activity of enzymes, however, prior art teaches specific

immobilization of enzyme through antibody and the antibody retains enzymatic activity {see attached reference of Gunaratna et al. Biotechnol. Prog. 1992, Vol.8, pp268-274:specifically see fig. 2 (d)}.

Therefore, the restriction requirement is deemed proper and is made FINAL.

As a result of the election and the corresponding scope of the compound identified, claims 1-4, 8-9, 12, 17, 19, 22, 25-27, 30, 35-36, 39, 42-45, 48, 51-52, 55, 59, 61, 64, 67-70, 81 and 88 and remaining subject matter of 73, 80, 86 and 86 {i.e. substrate (b) and oxidized derivatives of substrate (a) and (b)} are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected inventions. The withdrawn subject matter of claims 73, 80, 86 and 86 {i.e. substrate (b) and oxidized derivatives of substrate (a) and (b)} is properly restricted as it differs materially in structure and in element from the elected subject matter supra so as to be patentably distinct there from. Examiner suggests that the non-elected claims cited supra and non-elected subject matter be canceled in response to this Office action to expedite prosecution.

2. Therefore, claims 73, 74, 78, 80, 82, 86-87 and 89 are examined on merits in this office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 73, 74, 78, 80, 82, 86-87 and 89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Step (b) of claim 73 recites "contacting the incubated sample with a substrate converted to free thiol product in the presence of enzymatically active Lp-PLA2". The step is vague and indefinite because it is confusing as well as unclear as to whether in step (b), the substrate is first converted to a free thiol product by the enzymatically active Lp-PLA2 before contacting with the incubated mixture of step (a) or the incubated mixture of step (a) is contacted with the substrate in the presence of the enzymatically active Lp-PLA2. Further the substrate is not recited as having any sulfur group and thus the production of free thiol product is unclear. Moreover, the measuring step of the free thiol product is unclear and it is also unclear as to how is the measuring is correlated with the enzymatically active lipoprotein-associated phospholipase A2 (Lp-PLA2) in a sample because in step (b) enzymatically active Lp-PLA2 is added (see the recitation "in the presence of enzymatically active Lp-PLA2") and thus how is the measuring of free thiol product is correlated with the presence/measuring of Lp-PLA2 in the sample is vague and indefinite.

Therefore, the claim also fails to interrelate essential elements of the invention and is incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted

structural cooperative relationships are: structural relationship between the substrate and the fee thiol product, the sequence of steps to the production of detectable product and the relationship of the measuring of free thiol product to the addition of Lp-PLA2 and the presence of Lp-PLA2 in the sample.

6. Claim 73 recites "contacting the incubated sample with a substrate converted to a free thiol product in the presence of enzymatically active Lp-PLA2" in step (b). The recitation "in the presence of enzymatically active Lp-PLA2" does not clearly indicate that the substrate is a substrate for Lp-PLA2 and the free thiol product is a product from the enzymatic action of Lp-PLA2 on the substrate and therefore, the relationship of the substrate to the presence of enzymatically active Lp-PLA2 in the is unclear.
7. Claim 86 recites "a substrate converted to a detectable product in the presence of Lp-PLA2". The recitation "in the presence of Lp-PLA2" does not clearly indicate that the substrate is converted to the detectable product by the enzymatic action of Lp-PLA2 and therefore, the relationship of the substrate to the presence of Lp-PLA2 is unclear. Therefore, the chemical structure of the "substrate" and the "detectable product" (i.e. converted substrate) is unclear. Is the product detectable by itself? Further, it is unclear whether "substrate converted to a detectable product" is meant for the kit having an isolated (i.e. purified) converted substrate or the kit comprises a mixture of the substrate and the Lp-PLA2 enzyme wherein some of the substrate is converted to a product (detectable product?).
8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 73, 74, 78, 80, 82, 86-87 and 89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 73 and 86 recites “a compound which reduces active thiol(s)". In the specification the only description for a compound which reduces active thiol(s) is DTNB. There is absolutely no guidance or description of any other compound in the specification for use as "a compound which reduces active thiol" that would be useful for the purpose and process as described in the method steps for detection of Lp-PLA2 in the sample.

During examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, 367 F.3d 1359, 136~), 70 USPQ2d 1827, 1834 (Fed. Cir. 2004). Therefore, the recitation “a compound which reduces active thiols(s)” can be interpreted as encompassing other thiol reducing agents such as DTT and mercaptoethanol. However, there is no written descriptive support and guidance for use of the reducing agents as described above for "a compound which reduces active thiols" in the specification for the method process as claimed in claim 73. There is no guidance as to whether the reducing agent

as described above would be useful in the detection method as claimed in claims 73 and 86. Therefore, the specification fails to provide sufficient support of the broad use of all reducing agent for the purpose of reducing active thiol(s) in the sample for the purpose of measuring Lp-PLA2 activity with the use of a substrate converted to free thiol product in the presence of enzymatically active Lp-PLA2.

The MPEP states that the purpose of written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject mater later claimed. The MPEP lists factors that can be used to determined if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." See MPEP § 2163. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. In re Glass, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). Examples and description should be of sufficient scope as to justify the scope of the claims.

Accordingly, it is deemed that the specification fails to provide adequate written description and clear guidance for all compounds encompassed by "a compound which reduces active thiol(s)" and does not reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 73, 74, 78, 80, 82 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farooqui *et al* (J. Lipid Res. 1984) in view of Murata *et al* (Chem. Pharm. Biol 1991).

Farooqui *et al* disclose a method for measuring enzymatically activity phospholipases in a sample comprising reaction of the sample with DTNB (i.e. a compound that reduces active thiol), adding a thioester substrate for the phospholipase and measuring formation of free thiol by their reaction with DTNB that produces a detectable thionitrobenzoate from DTNB (page 1557: line 27 of left column to line 33 of right column; Fig. 2 and the paragraph under the heading “DISCUSSION” on page 1560).

Farooqui *et al* do not mention measuring Lipoprotein-associated Phospholipase A2 (also known as Lp-PLA2 or PAF-AH).

Murata *et al* disclose thioester (2-thio-PAF) as substrates for PAF acetylhydrolase (PAF-AH). Murata *et al* teach that PAF acetylhydrolase activity in blood/serum is correlated with respiratory symptoms in asthmatic children. Murata *et al* further disclose that the substrate is useful for measuring PAF acetylhydrolase activity.

Therefore, given the fact that the thioester 2-thio-PAF as taught by Murata *et al* are useful as a substrate for PAF-AH, it would be obvious to one of ordinary skill in the art at the time the invention was made to consider using 2-thio-PAF of Murata *et al* in the method of Farooqui *et al* for spectrophotometric detection of PAF-AH in a sample with the expectation of detection of respiratory symptoms in asthmatic patient with a reasonable expectation of success. Reasonable expectation comes from the teaching of the mechanism of production of active thiol compounds from thioester substrates by phospholipases and detection of the thiol compounds by DTNB (Farooqui et al) and 2-thio-PAF as disclosed by Murata is one of the thioester substrate for PAF-AH.

With regard to claim 74, Murata *et al* teach that PAF acetylhydrolase activity in blood/serum is correlated with respiratory symptoms and thus detection of PAF acetylhydrolase activity in blood/serum would be obvious to one of ordinary skill in the art for diagnosis of asthmatic symptoms.

With regard to claims 76 and 78, Farooqui *et al* teach incubating the sample and reference with DTNB until the slope of the recorder tracing reaches zero but however do not mention the incubation temperature. However, incubation at room temperature or 37C would be obvious for PAF-AH acetylhydrolase as the enzyme is known to show enzymatic activity at these temperatures. Moreover, the adjustment of particular working conditions (such as incubation temperature and duration of incubation) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan and therefore obvious under 35 U.S.C. § 103(a).

With regard to claim 80, as described in the rejection above, combination of the references teach utilizing 2-thio PAF substrate for detection of PAF acetylhydrolase.

With regard to claim 82, Farooqui *et al* teach using reference (page 1557: lines 28-29) and thus comparing free thiol production of the sample to the reference sample would be obvious to one of ordinary skill in the art to avoid non-specific reading.

12. Claims 86, 87 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farooqui *et al* (J. Lipid Res. 1984) in view of Murata *et al* (Chem. Pharm. Biol 1991) as described above and further in view of Maret et al (US Patent 5,478,741).

See the above teaching of 2-thio PAF substrate and DTNB for detection of PAF acetylhydrolase.

The above references do not teach putting the assay components in a kit.

Maret et al disclose that components for carrying out immunoassay methods can be packaged in the form of a kit for convenience and such a kit may include an appropriate assay device, antibody reagents, reagents for development of the assay such as buffers and, if needed, reagents for detection of the chosen label (column 6, lines 16-21).

Therefore, since the packaging of components in a kit form is a well-known obvious expedient for ease and convenience in assay performance (Maret et al) and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to place the PAF-AH substrates and other necessary components in the kit for a matter of convenience as taught by the '741 patent.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Primary Examiner, Art Unit 1641